FORM-PTO-1390 (Rev. 10-96) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 23530-0003

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5): Unassigned 09/673139

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB99/01170	16 April 1999 (16.04.99)	17 April 1998 (17.04.98)

TITLE OF INVENTION
BONE IMPLANT

APPLICANT(S) FOR DO/EO/US
Peter Allen Revell and Cameron Rolfe Howlett

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and the PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (UNSIGNED)
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

    A certified copy of the British priority document, Application No. 9808189.6, filed 17 April 1998, was filed in the International Application and therefore, the claim for priority is believed to be complete.

529 Rec'd PCT/PTO 11 OCT 2000

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
Unassigned 09/673139	PCT/GB99/01170	23530-0003

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO $840.00 (970)		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $670.00 (956)		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $690.00 (958)		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00 (960)		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $96.00 (962)		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00	
Surcharge of **$130.00 (154)** for furnishing the oath or declaration later than 20 ☐ 30 ☐ months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 0.00	

Claims	Number Filed	Number Extra	Rate		
Total Claims	24 -20 =	4	X$18.00 (966)	$ 72.00	
Independent Claims	2 -3 =	0	X$78.00 (964)	$ 0.00	
Multiple dependent claim(s) (if applicable)			+$260.00 (968)	$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				$ 912.00	
Reduction for 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ 0.00	-
SUBTOTAL =				$ 912.00	
Processing fee of **$130.00 (156)** for furnishing the English translation later than 20 ☐ 30 ☐ months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0.00	
TOTAL NATIONAL FEE =				$ 912.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00 (581)** per property +				$ 0.00	
TOTAL FEES ENCLOSED =				$ 912.00	
				Amount to be: refunded	$
				charged	$

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 50-1390 in the amount of $ 912.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-1390. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Robin I. Teskin
NAME

35,030
REGISTRATION NUMBER

(09/99)

Patent
Attorney's Docket No. 23530-0003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Peter A. Revell and Cameron R. Howlett	)	**BOX PCT**
	)	
Application No. (Unassigned - corresponds to PCT/GB99/01170)	)	Attn: DO/EO/US
	)	
Filed: October 11, 2000	)	
	)	
For: BONE IMPLANT	)	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Application corresponds to International Application No. PCT/GB99/01170, filed April 16, 1999. It should be noted that amended claims 1-24 were filed in the International Application on July 19, 2000.

Prior to examination, kindly amend the above-identified Application as follows.

In the Claims

Claim 3, line 1, delete "or claim 2".

Claim 4, line 1, delete "or claim 2".

Claim 6, line 1, delete "any one of the preceding claims" and insert

–claim 1,–.

Claim 7, lines 1 to 2, delete "any one of the preceding claims" and insert

–claim 1–.

Claim 10, lines 1 to 2, delete "any one of the preceding claims" and insert –claim 1–.

Claim 11, lines 1 to 2, delete "any one of the preceding claims" and insert –claim 1–.

Claim 13, line 1, delete "any one of claims 1 to 10" and insert –claim 1–.

Claim 17, line 1, delete "any one of claims 15 or claim 16" and insert –claim 15–.

Claim 20, line 1, delete "any one of claims 14 to 19" and insert –claim 14–.

Claim 21, line 1, delete "any one of claims 14 to 20" and insert –claim 14–.

Remarks

The present amendments are made to eliminate multiple dependencies in the claims.

Favorable consideration on the merits is respectfully requested.

Respectfully submitted,

SHAW PITTMAN

By: _____
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Date: October 11, 2000

09/673139
529 Rec'd PCT/PTO 11 OCT 2000
PCT/GB99/01170

BONE IMPLANT

FIELD OF THE INVENTION

The present invention relates to a bone implant having improved bone ongrowth properties, and a method for treating a bone implant to improve these properties.

BACKGROUND TO THE INVENTION

A major problem in orthopaedic reconstruction surgery, and in particular in joint replacement surgery, relates to the need to anchor permanently an orthopaedic implant to the skeleton. Usually, whilst bone grows up to the orthopaedic implant, it does not become physically and chemically bonded to the implant.

There are several known methods for achieving anchoring of orthopaedic implants to the skeleton. According to one commonly-known method, a "cement" is used to increase the surface area of the implant thereby to increase its interlock with the bone. Acrylic cements are commonly used for this purpose. However, over extended periods of time, problems are encountered with deterioration of the cement and the consequent loosening of the bone implant from the skeleton.

Another known method for attempting to anchor orthopaedic implants to the skeleton involves designing the implant to have a beaded or porous surface so that bone growing towards the implant will provide an interference fitting between the implant and the ingrowing skeletal tissues (e.g. bone).

A third method for achieving anchoring of an orthopaedic implant into the skeleton involves the use of an implant that includes a coating of a bioactive material such as hydroxyapatite. Bioactive materials are materials that are capable of promoting bone growth onto the implant, and include materials such as fluoroapatite, tricalcium phosphate, glass ionomers and bioactive glass such as Bioglass and AW Glass Ceramic, in addition to hydroxyapatite (HA). Orthopaedic implants having HA coatings

currently provide more effective fusion of the implant with the skeleton than other known anchoring techniques.

Since the long term success of orthopaedic implants is highly dependent on the anchoring of the orthopaedic implant to the skeleton, many investigations have been made into other techniques for improving anchoring.

Previously published studies[1,2,3] have investigated whether modifying the surface chemistry of uncoated structures (some of which are suitable for use as orthopaedic implants) by the incorporation of cations such as magnesium (Mg^{++}) enhances the adhesion of human bone-derived cells to these uncoated structures in *in vitro* studies. Incorporation of cations into ceramic or metallic structures in these previous studies was accomplished by ion beam implantation (embedding), which enables the incorporation of the cations into the ceramic or metallic surface atomic layers without affecting the surface properties thereof. The studies resulted in mixed success.

Accordingly, there still exists a need to develop bone implants having improved bone ongrowth properties, and methods for manufacturing such bone implants.

SUMMARY OF THE INVENTION

According to the present invention there is provided a bone implant having a surface comprising a bioactive material, said bioactive material having incorporated therein ions from one or more of the groups of the period table consisting of groups IIA, IVA, VIIA and transition elements, said bioactive material being a material that is capable of promoting bone growth into and/or onto the bone implant, and said ions being capable of improving the bone ongrowth properties.

Preferably the ions are selected from one or more groups of the periodic table consisting of groups IIA, IVB, VIB, VIII, IB, IIB, IVA and VIIA.

Preferably, the bioactive material comprises hydroxyapatite, and preferably the ions are incorporated into the surface of the bone implant by ion beam implantation or cathodic arc deposition.

The inventors have conducted an *in vivo* study in order to investigate whether the incorporation of ions by ion beam implantation techniques into bioactive material coated metal/metal alloy and/or orthopaedic implants (specifically hydroxyapatite) enhances bone growth onto the orthopaedic implant. The inventors have surprisingly discovered that the addition of particular ions to these coatings greatly enhances bone ongrowth onto the implant when compared with conventional hydroxyapatite (HA) coated metal alloy orthopaedic implants.

The growth of human bone cells onto a surface depends critically on the nature of the surface. Accordingly, whilst it is possible to use methods other than ion beam implantation (embedding) of the ions into the surface of the bone implant (e.g. cathodic arc deposition or formulating the surface of the bone implant to include such ions during formation of the bone implant), ion beam embedding is preferred since this method results in altering the surface chemistry of the surface material without affecting the surface structure and mechanical properties. Accordingly, if another method is used to provide a surface of a bone implant comprising a bioactive material having incorporated therein ions from one or more of the selected groups of the periodic table, care must be taken to ensure that the surface structure and mechanical properties of the surface are as close to the unmodified bioactive material surface properties as possible. The ions should be present in the surface of the bone implant at a level sufficient to achieve enhanced bone ongrowth but not at so great a level as to affect the mechanical and surface properties of the surface.

Preferably, the ions are incorporated into the surface of the bone implant up to a maximum depth of 200nm. Whilst this is the preferred maximum depth of ions, it is possible to implant ions

to greater depths, for example 1000nm. However, by implanting ions to these greater depths, there is an increasing risk that the surface and mechanical properties of the hydroxyapatite might be affected, due to the higher temperatures generated to achieve implantation of the ions to these depths. The higher temperatures are reached as a result of the greater energies used in ion beam implantation of the ions into the surface of the bioactive material.

Preferably, the ions are incorporated into the surface of the bone implant up to a maximum depth of 150nm, and preferably at depths ranging up to approximately 100nm.

Preferably, the ions are present in the surface of the bone implant at a level of between 1 x 10^{14} and 1 x 10^{18} ions per cm^2 of the surface. These dosage levels correspond to ion beam implantation energies up to approximately 100 kV.

Preferably the ions incorporated into the surface of the bone implant comprise the ions of elements that can form divalent cations, with the exception of silicon. Examples of such ions include the cations of iron, including ferrous and ferric ions, since iron is capable of forming the divalent ferrous cation.

Preferably, the ions incorporated into the surface of the bone implant comprise cations that are involved in metabolic processes in trace amounts.

Preferably the ions incorporated into the surface of the bone implant comprise one or more of the following:

magnesium, calcium, strontium, titanium, chromium, manganese, iron, copper, zinc, silicon and fluorine ions.

Preferably, the ions incorporated into the surface of the bone implant are from one or more of the groups of the periodic table consisting of groups IIA, VIIB, IIB, IVA and VIIA.

More preferably, the ions comprise magnesium, manganese, zinc or silicon ions.

In the case of a bone implant for use in total joint replacements, such as hip replacements, the bone implant will usually comprise a body portion coated with a hydroxyapatite coating. It is preferred that the body portion be formed of a metal or metal alloy, such as cobalt-chrome or titanium alloy. In the case of dental implants, the body portion may comprise a pin formed of a metal alloy coated by a hydroxyapatite coating, which is inserted into the jaw to replace a tooth.

However, it is not always necessary to use a body portion in the bone implant. The present inventors have found that it is also possible to use a bioactive material such as hydroxyapatite without a structural body portion to promote healing in a bone. According to the present invention there is also provided a bone implant wherein the bone implant substantially comprises a bioactive material (preferably hydroxyapatite) and no body portion. In this case, the bone implant is preferably in a granular form. The granular bioactive material embedded with ions of the selected groups of the periodic table can be used in the mending of fractured or defective bones. The granular ion beam implanted hydroxyapatite bone implant material can be packed into the area of the break or defect in the bone. Since this material has excellent bone growth enhancing properties, this material can be advantageously used to speed up the process of bone repair.

According to the present invention there is also provided a method of treating a bone implant having a surface comprising a bioactive material to improve the bone ongrowth properties of the bone implant, comprising subjecting the bone implant to ion beam implantation to thereby incorporate ions from one or more of the groups of the periodic table consisting of groups IIA, IVA, VII A and transition elements into the surface thereof.

Preferably the ions are selected from one or more groups of the periodic table consisting of groups IIA, IVB, VIB, VIII, IB, IIB, IVA and VIIA.

Preferably, the bioactive material comprises hydroxyapatite.

Preferably, the ions are incorporated into the surface of the bone implant at a level of between 1 x 10^{14} and 1 x 10^{18} ions per cm^2 of the surface.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows the percentage of bone ingrowth into an implant slot after 6 weeks of implantation in rabbit femur using an implant according to the invention as compared with a prior art implant.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will now be described in further detail by reference to the following *in vivo* experimental implantation study.

Cylindrical titanium alloy implants (Ti6Al4V) (4.5 diam x 6mm length) with a slot (2 x 2 x 4 mm) in one side were plasma-spray HA-coated at the bottom of the slot (HA-Ti6Al4V). Identically prepared cylinders were additionally ion beam implanted with Mg^{++} on the HA-coated region using a metal vapour vacuum arc (MEVVA) ion source (Mg-HA-Ti6Al4V) (1 x 10^{17} ions/cm^2Mg^{++}). Surgical implantation was performed under general anaesthetic with full sterile precautions into the lateral side of the lower femur of female NZ white rabbits (n=6). A 4.5 mm diameter hole was made using a saline cooled diamond-impregnated trephine and the sterile cylinders (autoclave, 121°C, 15 mins) inserted bilaterally. HA-Ti6Al4V was implanted on the left, Mg-HA-Ti6Al4V on the right. Fluorescent bone labels (tetracycline, calcein blue, calcein green, alizarin red) were administered at weekly intervals and animals killed at 6 weeks. Retrieved femurs were

processed in resin and ground sections (30μm) prepared with the implant *in situ* (Exakt System, Hamburg, Germany). The maximum distance that each label had reached in the slots was measured by fluorescence microscopy using an eye-piece graticule and the result expressed as percentage bone ingrowth. The area occupied by new bone after 6 weeks was measured in toluidine blue stained sections using a Quantimet 500 (Leica, Cambridge, UK) and expressed as percentage area of bone formation.

Results and Discussion

The percentage of bone ingrowth was significantly higher in Mg-HA-Ti6Al4V than in HA-Ti6Al4V implants at 3, 4 and 5 weeks ($p<0.05$)(Student's 't' test) (see Fig. 1). No significant differences were found at 1 and 2 weeks, though Mg-HA-Ti6Al4V mean values were higher. At 6 weeks, the percentage area of bone formation was significantly greater in the slots with Mg-HA-coating (25.73 ±9.12%, n=5) compared with HA-coating alone (5.86±3.46%, n=5)($p<0.05$, Student's 't' test).

These results demonstrate that Mg^{++} ion embedding of an HA-coating increases bone growth into a slot in a Ti6Al4V alloy implant when compared with conventional HA.

As will be appreciated by persons skilled in the art of the invention, whilst the experimental implantation study was conducted using magnesium ion embedding, other ions from the groups of the periodic table consisting of groups IIA, IVA, VIIA and transition elements will also result in enhanced bone formation when compared with conventional HA-coated implants. It will also be appreciated by persons skilled in the art of the invention that ions deleterious to bone mineralisation, such as aluminium (which is implicated in various bone diseases), would not result in enhancement of bone formation. The studies of the present inventors confirm that aluminium and other ions deleterious to bone mineralisation cannot be used in the present invention to increase bone formation.

References

1. Walsh WR, Zou L, Lefkoe TP, Kelly JC and Howlett CR (1992). Bone cell response to ion implanted silicon wafers. Mat Res Soc Symp 252:213-220.

2. Howlett CR, Evans MDM, Wildish KL, Kelly JC, Fisher LR, Francis GW and Best DJ (1993). The effect of ion implantation on cellular adhesion. Clinical Materials 14:57-64.

3. Howlett CR, Zreiqat H, Noorman H, Evans PA, Dalton BA, O'Dell R, McFarland C and Steele JC (1994). The effect of magnesium ion implantation into alumina upon the adhesion of human bone derived cells. J Materials Science: Materials in Medicine 5:715-722.

CLAIMS:

1. A bone implant having a surface comprising a bioactive material, wherein:

(a) the bioactive material has incorporated therein ions from one or more of the groups of the periodic table consisting of groups IIA, IVA, VIIA and transition elements;

(b) the ions are incorporated into or onto the surface of the bone implant by ion beam implantation or cathodic arc deposition; and

(c) the bioactive material is a material that is capable of promoting bone growth onto the bone implant.

2. The bone implant as claimed in claim 1, wherein the bioactive material comprises hydroxyapatite.

3. The bone implant as claimed in claim 1 or claim 2, wherein the ions are incorporated into the surface atomic layers of the bone implant up to a maximum depth of 200nm.

4. The bone implant as claimed in claim 1 or claim 2, wherein the ions are incorporated into the surface of the bone implant up to a maximum depth of 150 nm.

5. The bone implant as claimed in claim 4, wherein the ions are incorporated into the surface at depths ranging up to approximately 100nm.

6. A bone implant as claimed in any one of the preceding claims wherein the ions are present at a level of between 1×10^{15} and 1×10^{18} ions per cm^2 of the surface.

7. A bone implant as claimed in any one of the preceding claims, wherein the ions are selected from one or more groups of the periodic table consisting of groups IIA, IVB, VIB, VIIB, VIII, IB, IIB, IVA and VIIA.

8. A bone implant as claimed in claim 7, wherein the ions comprise one or more of the following:

magnesium, calcium, strontium, titanium, chromium, manganese, iron, copper, zinc, silicon and fluorine ions.

9. A bone implant as claimed in claim 7, wherein the ions incorporated into the surface of the bone implant are from one or more of the groups of the periodic table consisting of groups IIA, VIIB, IIB, IVA and VIIA.

10. A bone implant as claimed in any one of the preceding claims, wherein the ions comprise magnesium, manganese, zinc or silicon ions.

11. A bone implant as claimed in any one of the preceding claims, comprising a body portion coated with a bioactive material coating.

12. A bone implant as claimed in claim 11, wherein the body portion is formed of a metal or a metal alloy, preferably a titanium alloy.

13. A bone implant as claimed in any one of claims 1 to 10, wherein the bone implant substantially comprises a bioactive material.

14. A bone implant as claimed in claim 13, wherein the bone implant is in granular form.

15. A method of treating a bone implant having a surface comprising a bioactive material to improve the bone ongrowth properties of the bone implant comprising subjecting the bone implant to ion beam embedding thereby to incorporate ions from one or more of the groups of the periodic table consisting of groups IIA, IVA, VIIA and transition elements into the surface.

16. The method as claimed in claim 15, wherein the bioactive material comprises hydroxyapatite.

17. The method as claimed in any one of claim 15 or claim 16, wherein the ions are incorporated into the surface up to a maximum depth of 200nm.

18. The method as claimed in claim 17, wherein the ions are incorporated into the surface up to a maximum depth of 150nm.

19. The method as claimed in claim 18, wherein the ions are incorporated at depths ranging up to approximately 100nm.

20. The method as claimed in any one of claims 14 to 19, wherein the ions are present at between 1×10^{10} and 1×10^{18} ions per cm^2 of the implant surface.

21. The method as claimed in any one of claims 14 to 20, wherein the ions are selected from one or more groups of the periodic table consisting of groups IIA, IVB, VIB, VIIB, VIII, IB, IIB, IVA and VIIA.

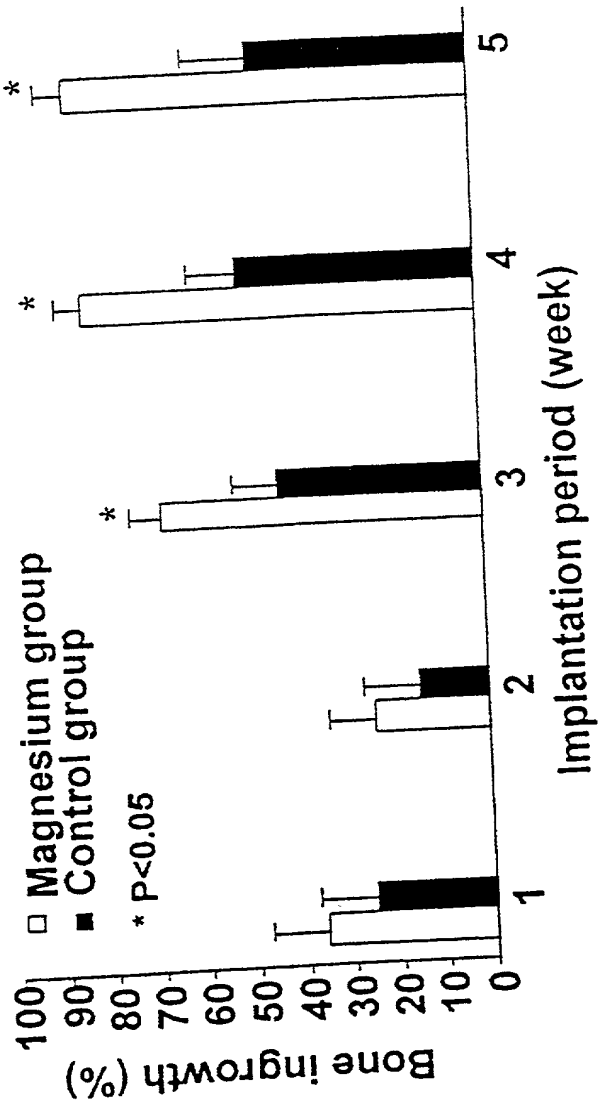
22. The method as claimed in claim 21, wherein the ions comprise one or more of the following:

magnesium, calcium, strontium, titanium, chromium, manganese, iron, copper, zinc, silicon and fluorine ions.

23. The method as claimed in claim 21, wherein the ions incorporated into the surface of the bone implant are from one or more of the groups of the periodic table consisting of groups IIA, VIIB, IIB, IVA and VIIA.

24. The method as claimed in claim 23, wherein the ions comprise magnesium, manganese, zinc or silicon ions.

FIGURE 1


Bone ingrowth (%)
0
10
20
30
40
50
60
70
80
90
100
1
2
3
4
5
Implantation period (week)
□ Magnesium group
■ Control group
* P<0.05
*
*
*

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION	Attorney's Docket No.

As a below-named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name;
I BELIEVE I AM THE ORIGINAL, FIRST AND SOLE INVENTOR (if only one name is listed below) OR AN ORIGINAL, FIRST AND JOINT INVENTOR (if more than one name is listed below) OF THE SUBJECT MATTER WHICH IS CLAIMED AND FOR WHICH A PATENT IS SOUGHT ON THE INVENTION ENTITLED:

BONE IMPLANT

the specification of which

(check one) ☐ is attached hereto;

☒ was filed on October 11, 2000 as

Application No. _____

and was amended on _____; (if applicable)

I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE;

I ACKNOWLEDGE THE DUTY TO DISCLOSE TO THE OFFICE ALL INFORMATION KNOWN TO ME TO BE MATERIAL TO PATENTABILITY AS DEFINED IN TITLE 37, CODE OF FEDERAL REGULATIONS, Sec. 1.56 (as amended effective March 16, 1992);

I do not know and do not believe the said invention was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to said application; that said invention was not in public use or on sale in the United States of America more than one year prior to said application; that said invention has not been patented or made the subject of an inventor's certificate issued before the date of said application in any country foreign to the United States of America on any application filed by me or my legal representatives or assigns more than twelve months prior to said application;

I hereby claim foreign priority benefits under Title 35, United States Code §119 and/or §365 of any foreign application(s) for patent or inventor's certificate as indicated below and have also identified below any foreign application for patent or inventor's certificate on this invention having a filing date before that of the application(s) on which priority is claimed:

COUNTRY/INTERNATIONAL	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
Great Britain	9808189.6	17 April 1998	YES X NO_
			YES_ NO_

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NO.	FILING DATE

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS (patented, pending, abandoned)
PCT/GB99/01170	16 April 1999	pending

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

2 Robin L. Teskin (Reg. No. 35,030)
Bonnie Weiss (Reg. No. ~~43,255~~)

Samir Elamrani (Reg. No. 43,601)

and: _____

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FULL NAME OF SOLE OR FIRST INVENTOR	SIGNATURE	DATE
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FULL NAME OF SECOND JOINT INVENTOR, IF ANY	SIGNATURE	DATE
Cameron Rolfe Howlett	C Howlett	16/Jan 2001
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POST OFFICE ADDRESS		
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FULL NAME OF THIRD JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF FOURTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF FIFTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF SIXTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF SEVENTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF EIGHTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		